

We Claim:

1. A method for inhibiting bone metastases and metastatic growth in a patient which comprises
5 administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

2. The method of Claim 1 wherein the bone
10 metastases are osteoblastic.

3. The method of Claim 2 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney,
15 thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

4. The method of Claim 3 wherein the primary cancer is prostate cancer and the patient is male.

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5. The method of Claim 1 which additionally comprises co-administration of an anticancer drug.

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6. The method of Claim 5 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

7. The method of Claim 1 which additionally comprises the administration of radiation therapy.

8. The method of Claim 1 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

15

9. The method of Claim 8 wherein the therapeutic agent is a bisphosphonate.

10. The method of Claim 1 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

11. A method for the inhibition of bone loss in a

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patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

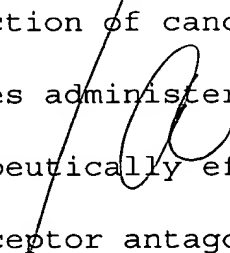
5 12. The method of Claim 11 wherein the patient has cancer.

10 13. The method of Claim 11 wherein the cancer is prostate cancer and the patient is male.

15 14. The method of Claim 11 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

20 15. The method of Claim 14 wherein the therapeutic agent is a bisphosphonate.

 16. A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.



17. The method of Claim 16 wherein the cancer is prostate cancer and the patient is male.

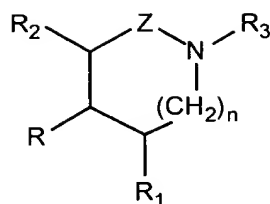
18. The method of Claim 16 which additionally
5 comprises the administration of an anticancer drug.

19. The method of Claim 18 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D
10 analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

20. The method of Claim 17 which additionally
15 comprises the administration of radiation therapy.

21. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a
20 compound of formula I:

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I

wherein

R is $-(CH_2)_m-W$;

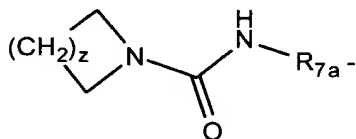
5 Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

R₁ and R₂ are independently selected from hydrogen,
 loweralkyl, alkenyl, alkynyl, alkoxyalkyl,
 alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl,
 haloalkoxyalkyl, alkoxyalkoxyalkyl,
 10 thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl,
 aminocarbonylalkyl, alkylaminocarbonylalkyl,
 dialkylaminocarbonylalkyl, aminocarbonylalkenyl,
 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl,
 hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl,
 15 arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl,
 alkylsulfonylamidoalkyl, heterocyclic,
 (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{CC}-$,

with the proviso that one or both of R₁ and R₂ is
other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)₂-R₇- R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-;

R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-

R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀-;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

5 R₁₁ and R₁₂ are independently selected from

hydrogen, loweralkyl, haloalkyl, alkoxyalkyl,

haloalkoxyalkylalkenyl, alkynyl, cycloalkyl,

cycloalkylalkyl, aryl, heterocyclic, arylalkyl,

(heterocyclic)alkyl, hydroxyalkyl, alkoxy,

10 aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl,

dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and
dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

15 R₁₅ is selected from amino, alkylamino and
dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and
dialkylamino;

R₁₇ is loweralkyl;

20 R₁₈ and R₁₉ are independently selected from hydrogen
and loweralkyl;

R₂₀ is selected from hydrogen, loweralkyl, alkenyl,

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R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and

R₂₂ is selected from a carboxy protecting group and heterocyclic;

10 R₂₄ is selected from hydrogen and loweralkyl;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

20 R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

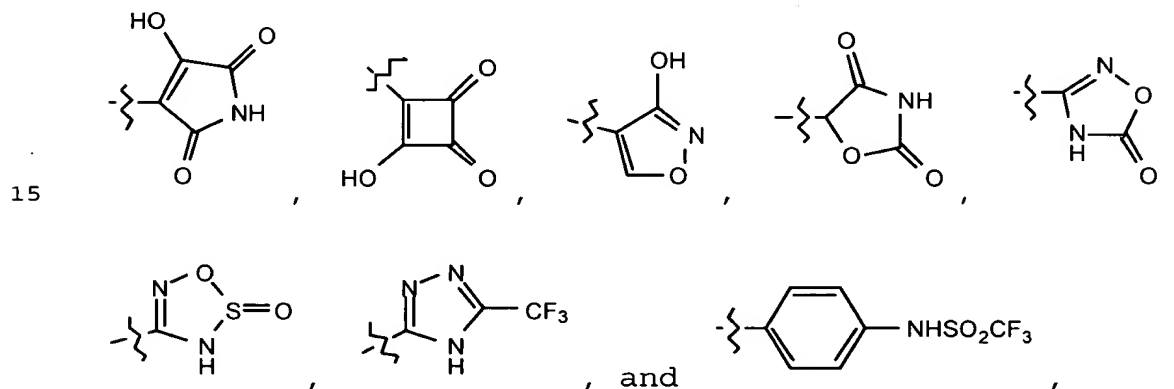
5 n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

10 G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$, $-CN$, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,



or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21 wherein the bone metastases are osteoblastic.

23. The method of Claim 22 wherein the osteoblastic
5 bone metastases result from the spread of a primary
cancer selected from breast, prostate, lung, kidney,
thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and
ovarian.

10 24. The method of Claim 23 wherein the primary
cancer is prostate cancer and the patient is male.

25. The method of Claim 21 which additionally
comprises the administration of an anticancer drug.

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26. The method of Claim 25 wherein the additional
anticancer drug is selected from leuprolide, goserelin,
bicalutamide, nilutamide, flutamide, vitamin D, vitamin D
analogues, estrogen, estrogen analogues, prednisone,
20 hydrocortisone, ketoconazole, cyproterone acetate, and
progesterone.

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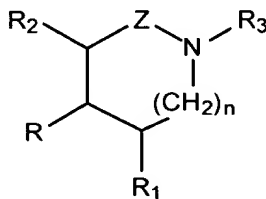
27. The method of Claim 21 which additionally comprises the administration of radiation therapy.

28. The method of Claim 21 which additionally
5 comprises the administration of at least one therapeutic agent which impedes net bone loss.

29. The method of Claim 28 wherein the therapeutic agent is a bisphosphonate.

10

30. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



15

I

wherein

R is $-(\text{CH}_2)_m\text{-W}$;

Z is selected from $-\text{C}(\text{R}_{18})(\text{R}_{19})-$ and $-\text{C}(\text{O})-$;

20 R_1 and R_2 are independently selected from hydrogen,

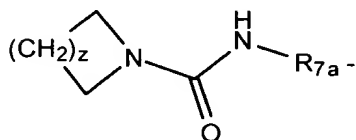
loweralkyl, alkenyl, alkynyl, alkoxyalkyl,
 alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl,
 haloalkoxyalkyl, alkoxyalkoxyalkyl,
 thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl,
 5 aminocarbonylalkyl, alkylaminocarbonylalkyl,
 dialkylaminocarbonylalkyl, aminocarbonylalkenyl,
 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl,
 hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl,
 arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl,
 10 alkylsulfonylamidoalkyl, heterocyclic,
 (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R_1 and R_2 is
 other than hydrogen;

R_3 is selected from $R_4-C(O)-R_5-$, $R_4-R_{5a}-$, $R_4-C(O)-$
 15 $R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$, $R_{26}-S(O)-R_{27}-$, $R_{22}-O-C(O)-R_{23}-$,
 loweralkyl, alkenyl, alkynyl, cycloalkyl,
 cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl,
 heterocyclic, (heterocyclic)alkyl, alkoxyalkyl,
 alkoxyalkoxyalkyl, and $R_{13}-C(O)-CH(R_{14})-$;

20 R_4 and R_6 are independently selected from
 $(R_{11})(R_{12})N-$, loweralkyl, alkenyl, alkynyl, cycloalkyl,
 cycloalkylalkyl, aryl, arylalkyl, heterocyclic,

(heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



5

R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

10

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀-;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

15

R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy,

20

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aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl,
dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and
dialkylamino;

5 R₁₄ is selected from aryl and R₁₅-C(O)-;

R₁₅ is selected from amino, alkylamino and
dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and
dialkylamino;

10 R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen
and loweralkyl;

R₂₀ is selected from hydrogen, loweralkyl, alkenyl,
haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and
15 cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl,
haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and
arylalkyl;

R₂₂ is selected from a carboxy protecting group and
20 heterocyclic;

R₂₃ is selected from covalent bond, alkylene,
alkenylene and -N(R₂₄)-R₂₅-;

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R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl,
alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,
5 heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and
alkoxy-substituted haloalkyl;

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

10 R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

15 R_{cc} is alkylene;

m is 0-6;

n is 0 or 1;

z is 0-5;

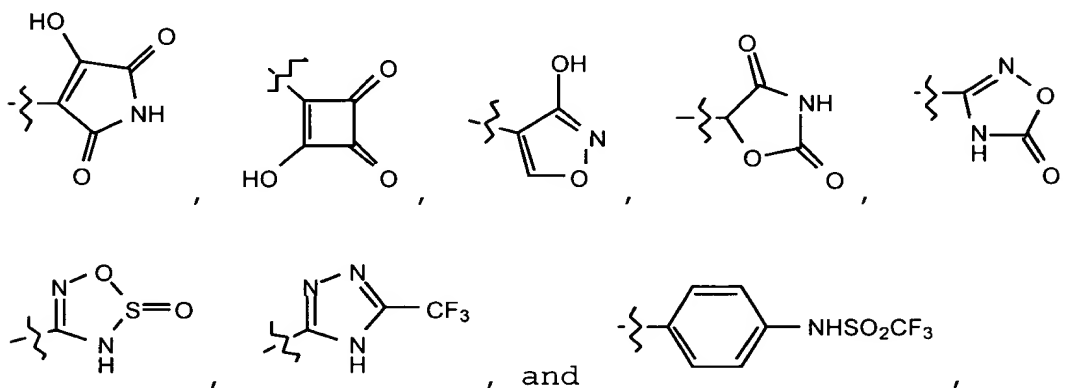
E is selected from hydrogen, loweralkyl and
20 arylalkyl;

G is selected from hydrogen and a carboxy protecting

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group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$,
 $-CN$, $-C(O)NHR_{17}$, alkylaminocarbonyl,
dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy,
5 sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,



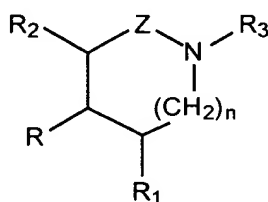
or a pharmaceutically acceptable salt thereof.

10 31. The method of Claim 30 wherein the cancer is prostate cancer and the patient is male.

32. The method of Claim 30 which additionally
comprises the administration of at least one therapeutic
15 agent which impedes net bone loss.

33. The method of Claim 32 wherein the therapeutic agent is a bisphosphonate.

34. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound
 5 of formula I:



I

wherein

R is $-(CH_2)_m-W$;

10 Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

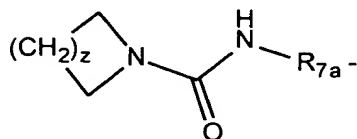
R₁ and R₂ are independently selected from hydrogen,
 loweralkyl, alkenyl, alkynyl, alkoxyalkyl,
 alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl,
 haloalkoxyalkyl, alkoxyalkoxyalkyl,
 15 thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl,
 aminocarbonylalkyl, alkylaminocarbonylalkyl,
 dialkylaminocarbonylalkyl, aminocarbonylalkenyl,
 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl,
 hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl,
 20 arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl,

alkylsulfonylamidoalkyl, heterocyclic,
(heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R_1 and R_2 is
other than hydrogen;

5 R_3 is selected from $R_4-C(O)-R_5-$, $R_4-R_{5a}-$, $R_4-C(O)-$
 $R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$, $R_{26}-S(O)-R_{27}-$, $R_{22}-O-C(O)-R_{23}-$,
loweralkyl, alkenyl, alkynyl, cycloalkyl,
cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl,
heterocyclic, (heterocyclic)alkyl, alkoxyalkyl,
10 alkoxyalkoxyalkyl, and $R_{13}-C(O)-CH(R_{14})-$;

R_4 and R_6 are independently selected from
 $(R_{11})(R_{12})N-$, loweralkyl, alkenyl, alkynyl, cycloalkyl,
cycloalkylalkyl, aryl, arylalkyl, heterocyclic,
(heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl,
15 haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy,
alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl,
alkoxy, and



R_5 is selected from a covalent bond, alkylene,
20 alkenylene, $-N(R_{20})-R_8-$, $-R_{8a}-N(R_{20})-R_8-$, $-O-R_9-$, and

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R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

5 R10-, and -R10a-N(R21)-R10-;

R₉ is alkylene;

R_{11} and R_{12} are independently selected from

hydrogen, loweralkyl, haloalkyl, alkoxyalkyl,
haloalkoxyalkylalkenyl, alkynyl, cycloalkyl,
cycloalkylalkyl, aryl, heterocyclic, arylalkyl,
(heterocyclic)alkyl, hydroxyalkyl, alkoxy,
aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl,
dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

R₁₅ is selected from amino, alkylamino and
20 dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and

dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

5 R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and
10 arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

15 R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and
20 alkoxy-substituted haloalkyl;

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

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R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

5 R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

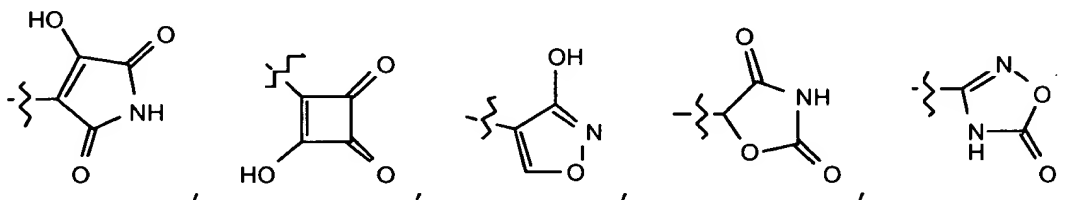
n is 0 or 1;

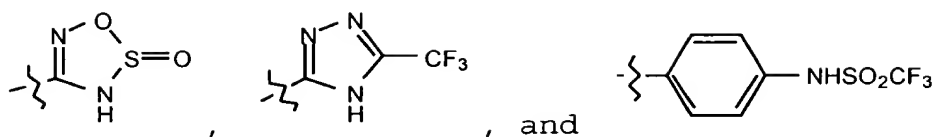
10 z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

15 W is selected from -C(O)₂-G; -PO₃H₂, -P(O)(OH)(E), -CN, -C(O)NHR₁₇, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)₂R₁₆, -S(O)₂NHC(O)R₁₆,





or a pharmaceutically acceptable salt thereof.

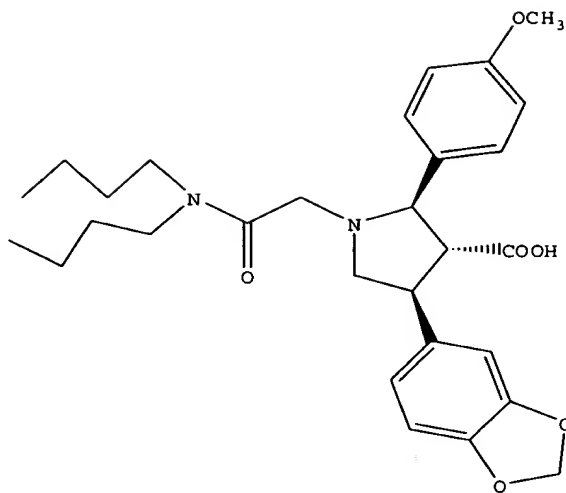
35. The method of Claim 34 wherein the cancer is
5 prostate cancer and the patient is male.

36. The method of Claim 34 which additionally
comprises the administration of an anticancer drug.

10 37. The method of Claim 36 wherein the additional
anticancer drug is selected from leuprolide, goserelin,
bicalutamide, nilutamide, flutamide, vitamin D, vitamin D
analogues, estrogen, estrogen analogues, prednisone,
hydrocortisone, ketoconazole, cyproterone acetate, and
15 progesterone.

38. A method for inhibiting bone metastases in a
patient which comprises administering to the patient in
need thereof a therapeutically effective amount of a
20 compound of formula III

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III.

39. The method of Claim 38 wherein the bone metastases are osteoblastic.

40. The method of Claim 39 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

41. The method of Claim 40 wherein the primary cancer is prostate cancer and the patient is male.

42. The method of Claim 40 which additionally comprises the administration of an anticancer drug.

43. The method of Claim 42 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

44. The method of Claim 40 which additionally comprises the administration of radiation therapy.

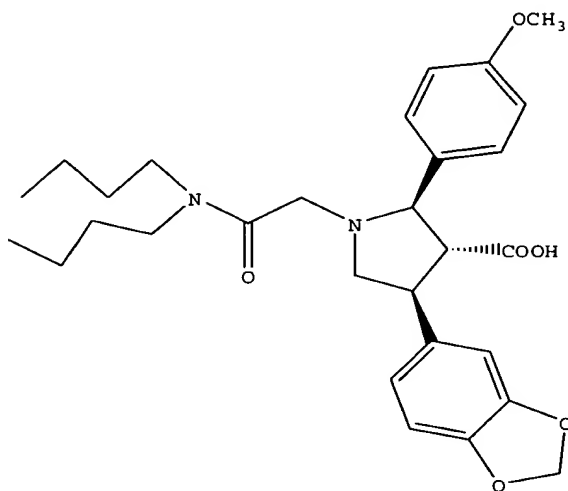
45. The method of Claim 40 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

46. The method of Claim 45 wherein the agent is a bisphosphonate.

47. The method of Claim 40 wherein the endothelin antagonist is an ET_A -selective endothelin antagonist.

48. A method for the inhibition of bone loss in

cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III



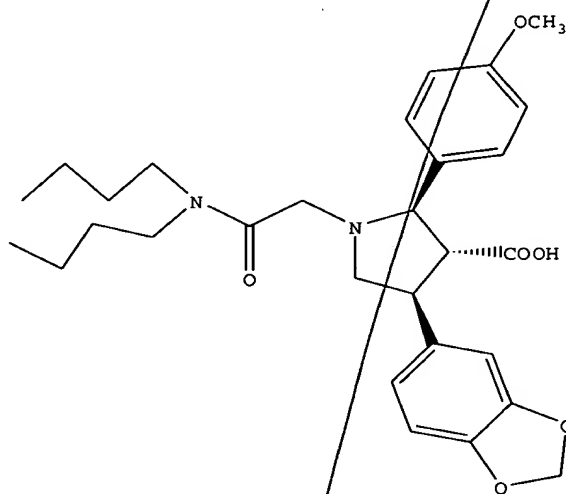
III.

49. The method of Claim 48 wherein the cancer is prostate cancer and the patient is male.

50. The method of Claim 48 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

51. The method of Claim 50 wherein therapeutic agent is a bisphosphonate.

52. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula III



III.

53. The method of Claim 52 wherein the cancer is prostate cancer and the patient is male.

54. The method of Claim 52 which additionally comprises the administration of an anticancer drug.

55. The method of Claim 54 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D

analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, ~~cyp~~roterone acetate, and progesterone.

5 56. A method for preventing new bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

10 57. A method for inhibiting metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

15 58. A method for inhibiting bone turnover in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.